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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

GRASS et al.

Art Unit: 1631

Serial No.: 09/786,361

Filed: March 14, 2001

Attorney Docket No. 109904-00015

For: PHARMACOKINETIC-BASED DRUG DESIGN TOOL AND METHOD

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
Washington, D.C. 20231
Sir:

July 17, 2001

Pursuant to 37 CFR §1.56, the attention of the Patent and Trademark Office is hereby directed to the information item(s) listed on the attached PTO-1449. Unless otherwise indicated herein, one copy of each item(s) is attached. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the item(s) be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

1. This Information Disclosure Statement is being filed (a) within three months of the U.S. filing date, OR (b) before the mailing date of a first Office Action on the merits in the present application, OR (c) accompanies a Request for Continued Examination. No certification or fee is required.
2. The Examiner's attention is directed to co-pending U.S. Patent Application Nos. 09/786,362 filed March 14, 2001; 09/320,544 filed May 26, 1999, 09/320,545, filed May 26, 1999; 09/320,371, filed May 26, 1999; 09/320,069, filed May 26, 1999; 09/320,270 filed May 26, 1999; and 09/320,372 filed May 26, 1999, which are directed to related technical subject matter. The identification of these U.S. Patent Applications are not to be construed as a waiver of secrecy as to those applications now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination of the present application.

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3. In addition to the references already cited in this application, those cited in the applications identified above, and those cited in the associated PCT applications (international search reports, written opinions, and preliminary examination reports are included in this IDS), Applicants, due to the number of references cited, would like to point out that an article by one of the inventors, Grass, George, "Simulation models to predict oral drug absorption from in vitro data", Advanced Drug Delivery Reviews, (1997) Vol. 23, pp. 199-219, appears to be one of the more relevant references.

Respectfully submitted,



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Section A

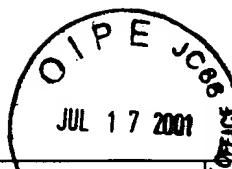
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Section B

<u>APPLICATION SERIAL NUMBER</u>	<u>FILING DATE</u>	<u>STATUS</u>
09/320,069	26 May 1999	Pending
09/320,270	26 May 1999	Pending
09/320,371	26 May 1999	Pending
09/320,372	26 May 1999	Pending
09/320,544	26 May 1999	Pending
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LIST OF REFERENCES CITED BY APPLICANT

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AA	Artursson et al., "Caco-2 Monolayers in Experimental and Theoretical Predictions of Drug Transport", <u>Advanced drug Delivery Reviews</u> (1996) Vol. 22, pp 67-84
AB	Audus et al., "The Use of Cultured Epitheelial and Endothelial Cells for Drug Transport and Metabolism Studies", <u>Pharmaceutical Research</u> (1990) Vol. 7, No. 5, pp 435-451
AC	Bailey et al., "The Use of the Intestinal Epithelial Cell Culture Model, Caco-2 in Pharmaceutical Development", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22 pp. 85-103
AD	de Boer et al., "Reconstitution of the Blood-Brain Barrier in Cell Culture for Studies of Drug Transport and Metabolism", <u>Advanced Drug Deliver Reviews</u> (1996) Vol. 22, pp. 251-264
AE	Friedberg et al., "Recombinant DNA Technology as an Investigative Tool in Drug Metabolism Research", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22, pp. 187-213
AF	Grass et al., "Mechanisms of Corneal Drug Penetration III: Modeling of Molecular Transport", <u>Journal of Pharmaceutical Sciences</u> , (1988) Vol. 77, No. 1, pp. 24-26
AG	Grass et al., "In Vitro Measurement of Gastrointestinal Tissue Permeability Using a New Diffusion Cell", <u>Pharmaceutical Research</u> (1988) Vol. 5, No. 6, pp. 372-376
AH	Hidalgo et al., "Characterization of the Unstirred Water Layer in Caco-2 Cell Monolayers Using a Novel Diffusion Apparatus", <u>Pharmaceutical Research</u> (1991) Vol. 8, No. 2, pp. 222-227
AI	Hidalgo et al., "Letter to the Editor: A New Side-by-Side Diffusion Cell for Studying Transport Across Epithelial Cell Monolayers", <u>In Vivo Cell. Dev. Biol.</u> (1992) Vol. 28A, pp. 578-580
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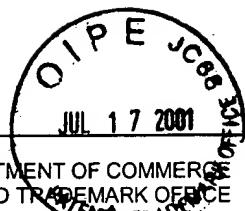
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	AK	Hu et al., "Membrane Permeability Parameters for Some Amino Acids and β -Lactam Antibiotics: Application of the Boundary Layer Approach", <u>J. Theor. Biol.</u> (1988) Vol. 131, pp. 107-114
	AL	Jezyk et al., "Permeability Characteristics of Various Intestinal Regions of Rabbit, Dog, and Monkey", <u>Pharmaceutical Research</u> (1992) Vol. 9, No. 12, pp. 1580-1586
	AM	Kou et al., "Calculation of the Aqueous Diffusion Layer Resistance for Absorption in a Tube: Application to Intestinal Membrane Permeability Determination", <u>Pharmaceutical Research</u> (1991) Vol. 8, No. 3, pp. 298-305
	AN	Kuhfeld et al., "In Vitro Measurement of Drug Transport Using a New Diffusion Chamber Compatible with Millicell Culture Supports: Performance with Caco-2 Monolayers", <u>International Journal of Pharmaceutics</u> (1996) Vol. 133, pp. 47-58
	AO	LeCluyse et al., "Strategies for Restoration and Maintenance of Normal Hepatic Structure and Function in Long-Term Cultures of Rat Hepatocytes", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22, pp. 133-186
	AP	Mathias et al., "Respiratory Epithelial Cell Culture Models for Evaluation of Ion and Drug Transport", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22, pp. 215-249
	AQ	Maurel, P., "The Use of Adult Human Hepatocytes in Primary Culture and other In Vitro Systems to Investigate Drug Metabolism in Man", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22, pp. 105-132
	AR	Pidgeon et al., "IAM Chromatography: An In Vitro Screen for Predicting Drug Membrane Permeability", <u>J. Med. Chem.</u> (1995) Vol. 38, pp. 590-594
	AS	Quaroni et al., "Development of Intestinal Cell Culture Models for Drug Transport and Metabolism Studies", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22, pp 3-52
	AT	Rubas et al., "Comparison of the Permeability Characteristics of a Human Colonic Epithelial (Caco-2) Cell Line to Colon of Rabbit, Monkey, and Dog Intestine and Human Drug Absorption", <u>Pharmaceutical Research</u> (1993) Vol. 10, No. 1, pp. 113-118

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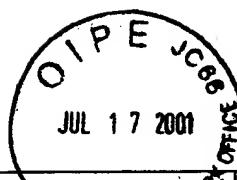
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AV	Abstract from <u>Pharmaceutical Research</u> (1996) Vol. 13, No. 9 - PDD 7039, McCarthy et al., "Automated Permeability Analysis of Mixtures Across Caco-2 Cell Monolayers" - page S-242
AW	Abstract from <u>Pharmaceutical Research</u> (1996) Vol. 11, No. 10 - APQ 1113, Kuhfeld et al., "An Automated In Vitro Permeability Screen Using Robotics", page S-39
AX	Abstract from <u>Pharmaceutical Research</u> (1995) Vol. 12, No. 9 - BIOTEC 2064, Augustijns et al., "Permeability Screen for Synthetic Peptide Combinatorial Libraries Using Caco-2 Cell Monolayers and LC/MS/MS", page S-94
AY	Aarons et al., "Computer-assisted Learning Lessons in Drug Disposition and Pharmacokinetics", <u>Journal of Pharmacological Methods</u> (1988) Vol. 20, pp. 109-123
AZ	Allen, G., "MODFIT: A Pharmacokinetics Computer Program", <u>Biopharmaceutics & Drug Disposition</u> (1990) Vol. 11, pp. 477-498
BA	Amidon et al., "Model-Independent Prediction Methods in Pharmacokinetics: Theoretical Considerations", <u>Mathematical Biosciences</u> (1975) Vol. 25, pp. 259-272
BB	Amidon et al., "A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In Vivo Drug Product Dissolution and In Vivo Bioavailability", <u>Pharmaceutical Research</u> (1995) Vol. 12, No. 3, pp. 413-420
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BE	Beckett et al., "A Model for Steroid Transport Across Biological Membranes", <u>J. Pharm. Pharmacol.</u> , (1975) Vol. 27, pp. 226-234
BF	Berger et al., "Combining Statistical, Rule-Based, and Physiologic Model-Based Methods to Assist in the Management of Diabetes Mellitus", <u>Computers and Biomedical Research</u> (1990) Vol. 23, pp. 346-357
BG	Blakey et al., "Quantitative Structure-Pharmacokinetics Relationships: I. Development of a Whole-Body Physiologically Based Model to Characterize Changes in Pharmacokinetics Across a Homologous Series of Barbiturates in the Rat", <u>Journal of Pharmacokinetics and Biopharmaceutics</u> , (1997) Vol. 25, No. 3, pp. 277-312
BH	Bois et al., "Bioequivalence: Performance of Several Measures of Extent of Absorption", <u>Pharmaceutical Research</u> (1994) Vol. 11, No. 5, pp. 715-722
BI	Bradshaw, J., "Prediction of Metabolism, Degradation and Toxicity of Xenobiotics", <u>Pesticide Sci.</u> , (1992) Vol. 34, No. 2, page 185
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BK	Cardot et al., "PKC, A New Pharmacokinetic Software Using SAS", <u>European Journal of Pharmaceutics and Biopharmaceutics</u> (1997) Vol. 43, pp. 197-199
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BM	Chiou, W.L., "Determination of Drug Permeability in a Flat or Distended Stirred Intestine", <u>International Journal of Clinical Pharmacology and Therapeutics</u> (1994) Vol. 32, No. 9, pp. 474-482
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BO	Conolly et al., "Biologically Based Pharmacodynamic Models: Tools for Toxicological Research and Risk Assessment", <u>Ann. Rev. Pharmacol. Toxicol.</u> (1991) Vol. 31, pp. 503-523
BP	Dijkstra et al., "Simulation of Nutrient Digestion, Absorption and Outflow in the Rumen: Model Description", <u>American Institute of Nutrition</u> (1992) pp. 2239-2256
BQ	Dong, M.H., "Microcomputer Programs for Physiologically-based Pharmacokinetic (PB-PK) Modeling", <u>Computer Methods and Programs in Biomedicine</u> (1994) Vol. 45, pp. 213-221
BR	Firmer et al., "Simulation of Gastrointestinal Drug Absorption I. Longitudinal Transport in the Small Intestine", <u>International Journal of Pharmaceutics</u> (1988) Vol. 48, pp. 231-246
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BT	Gex-Fabry et al., "Considerations on Data Analysis Using Computer Methods and Currently Available Software for Personal Computers" in <u>Handbook on Experimental Pharmacology</u> (1994) Vol. 110, pp. 507-527 (Chapter 13)
BU	Grass et al., "A Model to Predict Aqueous Humor and Plasma Pharmacokinetics of Ocularly Applied Drugs", <u>Investigative Ophthalmology & Visual Science</u> (1993) Vol. 34, No. 7, pp. 2251-2259
BV	Grass et al., "Evaluation of the Performance of Controlled Release Dosage Forms of Ticlopidine Using In Vitro Intestinal Permeability and Computer Simulations", <u>Journal of Drug Targeting</u> (1994) Vol. 2, pp. 23-33
BW	Grass, G.M., "Simulation Models to Predict Oral Drug Absorption from In Vitro Data", <u>Advanced Drug Delivery Reviews</u> (1997) Vol. 23, pp. 199-219
BX	Gomeni et al., 'IGPHARM: Interactive Graphic Package for Pharmacokinetic Analysis', <u>Computers and Biomedical Research</u> (1978) Vol. 11, pp. 345-361

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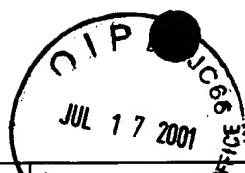
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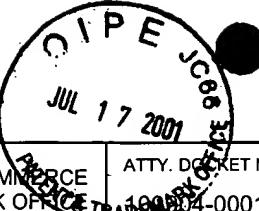
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BZ	Hampton et al., "Comparison of MS-DOS and Macintosh Pharmacokinetic Analysis Programs Using a Two-Compartment, Two-Infusion Dosing Scheme", <u>Clinical Pharmacy</u> (1991) Vol. 10, pp. 206-209
CA	Hayashi et al., "Pharmacokinetic Analysis of Cimetidine Plasma Concentration Data in Dogs Using a Two Phase Absorption Model", <u>Pharmaceutical Research</u> (1994) Vol. 11, No. 10, page S-420
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CE	Kalmaz, E.E., "Computer Modeling and Parameter Estimation for Pharmacokinetics and Toxicity Studies", <u>Journal of American College of Toxicology</u> (1996) Vol. 5, No. 6, page 607
CF	Keller et al., "Standardized Structure and Modular Design of a Pharmacokinetic Database", <u>Computer Methods and Programs in Biomedicine</u> (1988) Vol. 55, pp. 107-115
CG	Kirkup et al., "A Demonstration of Pharmacokinetics and Physiological Modelling Using a Microcomputer for Data Capture and Analysis", <u>Computer Applications in the Biosciences</u> (1986) Vol. 2, No. 4, pp. 277-282
CH	Kwon et al., "Theoretical Considerations on Two Equations for Estimating the Extent of Absorption After Oral Administration of Drugs", <u>Pharmaceutical Research</u> (1986) Vol. 13, No. 4, pp. 566-569

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CK	Leahy et al., "Physiologic Based Pharmacokinetic Modelling and QSAR", <u>Bioactive Compound Design: Possibilities for Industrial Use</u> , pp. 147-151
CL	Lincoln et al., "Pharmacokinetic Simulation: A Future Means for Better Control of Cancer Chemotherapy", <u>Recent Results in Cancer Research</u> , pp. 103-107
CM	Lu et al., "An Interactive Program for Pharmacokinetic Modeling", <u>Journal of Pharmaceutical Sciences</u> (1993) Vol. 82, No. 5, pp. 537-542
CN	Luner et al., "Description and Simulation of a Multiple Mixing Tank Model to Predict the Effect of Bile Sequestrants on Bile Salt Excretion", <u>Journal of Pharmaceutical Sciences</u> (1993) Vol. 82, No. 3, pp. 311-318
CO	Mazumdar et al., "A Mathematical Study of Simple Exponential Modelling in Biochemical Processes", <u>Australasian Physical & Engineering Sciences in Medicine</u> (1991) Vol. 14, No. 4, pp. 226-233
CP	Metzler et al., "Package of Computer Programs for Pharmacokinetic Modeling", <u>Biometrics, Journal of the Biometric Society</u> (1974) Vol. 30, No. 3, pp. 562-563
CQ	Metzler, C.M. "Commentary to 'Linear and Nonlinear System Approaches in Pharmacokinetics. How Much Do They Have To Offer? II. The Response Mapping Operator (RMO) Approach', <u>J. Pharmacokin, Biopharm</u> , (1988) Vol. 16, pp. 543-571
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	CU	Nogami et al., "Pharmacokinetic Analysis on the Disappearance of Ethoxybenzamide from Plasma. Statistical Treatment of Data of Two Compartmental Model by a Digital Computer", <u>Chem. Pharm. Bull.</u> (1969) Vol. 17, No. 10, pp. 2097-2104
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	CW	Pearce et al., "A Hybrid Computer System for Pharmacokinetic Modeling I. Software Considerations", <u>Proceedings of the 1981 Summer Computer Simulation Conference</u> (1981) pp. 117-121
	CX	Pearce et al., "PKDEMO - A Pharmacokinetic Demonstration Simulation Program", <u>Simulation</u> (1991) Vol. 56, No. 1, pp. 27-30
	CY	Powers et al., "Automated Processing of Data from Pharmacokinetic Investigations", <u>Computers and Biomedical Research</u> (1976) Vol. 9, pp. 543-548
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	DA	Ramsay et al., "Pharmacokinetic Simulations Using STELLA: Prediction of In Vivo Performance of Oral Dosage Forms", <u>Eur. J. Pharm. Biopharm.</u> (1991) Vol. 37, No. 3, pp. 192-197
	DB	Scaf, A.H.J., "Pharmacokinetic Analysis with Rugfit: An Interactive Pharmacokinetic Computer Program", <u>Biopharmaceutics & Drug Disposition</u> (1988) (1988) Vol. 9, pp. 415-446

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DQ	Zhang et al., "A Computer Model for Oral Transmucosal (OT) Bioavailability Prediction", <u>Pharmaceutical Research</u> (1997) Vol. 14, No. 10, page SA-662
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DS	Abstracts from <u>Pharmaceutical Research</u> (1995) Vol. 12, No. 9, page S-367 -- PPDM 8162, Yu et al., "Saturable Small Intestinal Drug Absorption in Humans: Modeling and Interpretation of Cefatrizine Data" and PPDM 8164, Heatherington et al., "A Pharmacokinetic-Pharmacodynamic Model to Predict Effect of Formulation of Lomustine on Medullat Blastoma Cells in the CSFC:A SAAM II Simulation"
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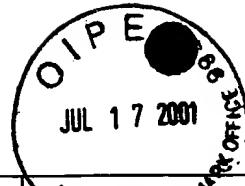
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DW	Rossum et al., "Pharmacokinetics: A Dynamic Systems Approach," <u>Drug Metabolism and Distribution</u> , Edited by Lamble, Amsterdam: Elsiver Press, pp. 159-167, 1983
DX	Harvey, "Drug Absorption, Action and Disposition," Remington's Pharmaceutical Sciences, Easton Pennsylvania: Mack Publishing Co., Chap. 35 pp. 697-724, 1990
DY	Harvey et al., "Basic Pharmacokinetics," Remington's Pharmaceutical Sciences, Easton Pennsylvania: Mack Publishing Co., Chap. 36, pp. 725-745, 1990
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EB	West Database Search Report for U.S. Patent No. 5,789,160 (Eaton et al.)
EC	Seydel, J.K. et al., "Quantitative Structure-Pharmacokinetic Relationships and Drug Design", <u>Pharma. Ther.</u> (1982), Vol. 15, pp. 131-181.
ED	Enstein, Kurt, "The Future of Toxicity Prediction with QSAR", <u>In Vitro Toxicology A Journal of Molecular and Cellular Toxicology</u> , (1993) Vol. 6, No. 3 pp. 162-169
EE	Abstract from <u>Pharmaceutical Research</u> (1994) Vol. 11, No. 10 - APQ 1113, Kuhfeld et al., "An Automated In Vitro Permeability Screen Using Robotics", page S-39

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	FB	5,789,160	08/04/98	Eaton et al.			
	FC	4,411,989	10/25/83	Grow	435	20	08/13/81
	FD	4,775,794	10/04/88	Behmann	250	373	11/02/87
	FE	4,952,061	08/28/90	Edgar	356	407	06/27/88
	FF	4,975,581	12/04/90	Robinson et al.	250	339	06/21/89
	FG	5,387,421	02/07/95	Amidon et al.	424	472	05/31/94
	FH	5,569,452	10/29/96	Amidon et al.	424	78.1	05/30/95

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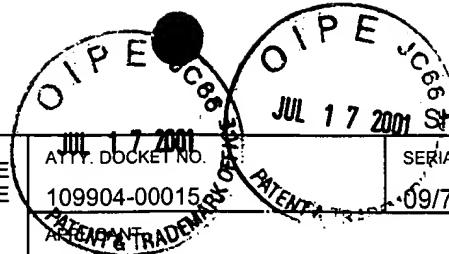
		DOCUMENT NO.	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION YES NO PART.
	FI	WO 94/23705	10/27/94	PCT	A61K	9/48	
	FJ	WO 96/13721	05/09/96	PCT	G01N	33/487	
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	GC	5,956,501	09/21/99	BROWN	395	500.32	
	GD	5,914,891	06/22/99	MCADAMS, et al.	364	578	
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	GI	EP 0 818 744 A2	01/14/98	EUROPE	A61K	9/48	
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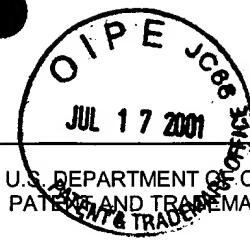
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	HD	5,657,255	08/12/97	FINK, et al.	364	578	
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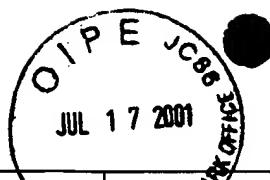
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EF	Notification of Transmittal of the International Search Report or the Declaration, November 1, 2000, International Application No. PCT/US99/21001
EG	Written Opinion, February 26, 2001, PCT/US99/21001
EH	Notification of Transmittal of International Preliminary Examination Report, December 14, 2000, International Application No. PCT/US99/21151
EI	Written Opinion, July 7, 2000, International Application No. PCT/US99/21151
EJ	Notification of Transmittal of the International Search Report or the Declaration, February 4, 2000, International Application No. PCT/US99/21151
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